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Gender Differences in Critical Illness and Critical Care Research



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KEYWORDS

• Gender • Female • Estrogen • Critical illness • Obstetrics • SARS-CoV-2 • Sepsis • ARDS

KEY POINTS

- Male patients gain admission to the intensive care unit and use resources in the intensive care unit more than female patients.
- Estrogen may have a protective effect in critical illness.
- Women receive less appropriate management of the acute respiratory distress syndrome than men.
- No consistent differences in sepsis outcomes by sex have been found, but women receive less timely initiation of antibiotics.
- Women are more likely to experience hypoactive delirium while in the intensive care unit and have worse functional outcomes after discharge.

INTRODUCTION

Research regarding the impact both social and genetic determinants of health play in admission to the intensive care unit (ICU) and outcomes from an ICU stay have gained traction in critical care literature in recent years. Determinants such as race and socioeconomic status are more commonly discussed; less explored is the impact of sex or gender on critical illness because women have historically been excluded from clinical trials or had limited participation, a problem that the US Food and Drug Administration has acknowledged previously and attempted to address.¹

It is vital to understand the impact of gender on admission to the ICU as well as the influence of sex in various disease states in order for ICU clinicians to be able to apply the principles of precision medicine to their patients admitted to the ICU. In this article, we explore the research into and the impact of gender on admission into the ICU and the use of ICU resources, gender dimorphism in sepsis, the impact of gender on acute respiratory

distress syndrome (ARDS), research regarding obstetrics critical care and outcomes, and the impact of gender on ICU mortality, delirium, and functional outcomes.

EPIDEMIOLOGY

Multiple epidemiologic studies have observed sex-related differences in admission to the ICU as well as the use of ICU resources. Many of these studies were performed in ICUs outside of the United States and have consistently demonstrated lower admission rates for women to ICUs despite similar severity of illness between men and women or even a greater severity of illness in women.^{2–7} In a study performed by Blecha and colleagues³ in Germany of more than 20,000 patients, male patients were more likely to undergo tracheostomy, dialysis, extracorporeal membrane oxygenation, and pulmonary artery catheter insertion despite similar severity of illness to female patients; additionally, the male patients had a longer duration of mechanical ventilation. Another study

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performed in Austria by Valentin and colleagues⁴ of more than 25,000 patients in 31 ICUs found that men were more likely to undergo invasive treatments with mechanical ventilation, vasopressor use, and intracranial pressure management compared with women, despite a higher severity of illness in women; this study also noted that 58.3% of patients admitted were male and 41.7% of admitted patients were female. This preponderance of males gaining admission to ICUs and using more ICU resources more than females may be due to several reasons. First, this difference may be a consequence of goals of care and end-of-life discussions; in a study by Sharma and colleagues,⁸ male patients with advanced cancer who had of end-of-life discussions were more likely to receive aggressive, nonbeneficial care in the ICU than women with advanced malignancies who also participated in end-of-life discussions. This finding has been observed similarly in a population of postoperative patients admitted to the ICU, where women were less likely than men to remain at full code status at ICU discharge and death and were also more likely to be discharged or die after a change in code status to do not resuscitate as compared with men.⁹ Interestingly, a study by Cooney and colleagues¹⁰ found that divorced women and widowed women were more likely to have advanced directives and more likely to have designated a medical power of attorney compared with their married counterparts; this was conjectured to be due to familiarity with the end-of-life process for widowed women and due to dependence on nonkin ties for divorced women. The consumption of ICU resources predominantly by male patients is conjectured to be related to the role of sex hormones in the immune response in critical illness, which is discussed further elsewhere in this article.¹¹

In the United States, studies have demonstrated that fewer women have been admitted to ICUs than men, despite higher severity of illness, although these studies are limited by their retrospective design.¹² Based on current epidemiologic studies of sex-related differences in admission to ICUs and the use of ICU resources, the questions of horizontal equity (equal use for equal need) and vertical equity (more treatment for those with greater need than those with lesser need) in relation to gender requires further research.

SEX HORMONES IN CRITICAL ILLNESS

Various in vitro and in vivo experimental models have shown gender differences in innate immune responses that may influence the trajectory of

illnesses requiring admission to the ICU, such as shock, trauma, and sepsis. One such experimental study by van Eijk and colleagues demonstrated increased proinflammatory state with increased tumor necrosis factor- α and C-reactive protein levels in female patients after injection of lipopolysaccharide to simulate endotoxemia.¹³ Estrogen has been suggested to be immunoprotective after trauma and severe blood loss, as well as in sepsis, whereas androgens have been demonstrated to suppress the immune system.^{14–17} This finding is further bolstered by studies that outcomes in trauma, shock, and sepsis are better for women than men younger than the age of 50, when the protective effect of estrogen is presumably still present.¹⁸ The findings in these studies are more complex than their conclusions; none of these gender-specific studies took oral contraceptives or hormone replacement therapy into account in investigating the outcomes in the critically ill patients. Furthermore, the cited studies did not account for variability in plasma sex hormone levels during menstrual cycles or menopause. The overall understanding of the impact of sex hormones on attenuating critical illness remains opaque at this time. The impact of sex-specific hormones in attenuating critical illness needs further research with specific attention to external factors impacting sex hormones.

GENDER DIFFERENCES IN ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is defined by the acute development of diffuse, bilateral pulmonary infiltrates after a direct or indirect lung injury with resultant hypoxemia, a $\text{PaO}_2\text{:Fio}_2$ ratio of less than 300 on positive end-expiratory pressure of 5 cm H_2O , and often requiring mechanical ventilation, as defined by the Berlin criteria.¹⁹ ARDS is further categorized into mild, moderate, and severe based on the $\text{PaO}_2\text{:Fio}_2$ ratio, with a $\text{PaO}_2\text{:Fio}_2$ of less than 300 defining mild, a $\text{PaO}_2\text{:Fio}_2$ of less than 200 defining moderate, and a $\text{PaO}_2\text{:Fio}_2$ of less than 100 defining severe disease.

Risk factors for the development of ARDS in the general population include direct lung injury—such as pneumonia, aspiration, drowning—and indirect lung injury through cytokine stimulation—such as trauma, sepsis, and pancreatitis. The development of ARDS is likely to be influenced by various mechanisms, including clinical, environmental, and genetic factors contributing to observed variations. Gender as a factor in the development of ARDS and ARDS outcomes is not well-studied. One study of critically injured patients who developed ARDS examined gender differences and found

that women were more likely than men to develop ARDS after a major trauma, despite adjusting for age, mechanism of injury, injury severity, and blood product transfusion.²⁰ In contrast, the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has demonstrated a male bias mortality with higher incidence of ARDS and ARDS-related mortality in males, conjectured to be related to higher production of IL-6 in males as well as estrogen-related downregulation of angiotensin-converting enzyme 2 receptors, which the SARS-CoV-2 exploits to gain entry into host cells.²¹ A higher incidence of death related to ARDS secondary to SARS and Middle East Respiratory Virus was also observed in males.^{22,23} A study of trends of ARDS in the United States from 1990 to 2013 found that males had a higher average age-adjusted mortality than females.²⁴ Overall, gender as a risk factor for and sex bias in the development of ARDS has not been shown consistently in epidemiologic studies, but male sex does seem to confer higher risk of ARDS-related mortality.

The management of ARDS is entirely supportive until the underlying process driving ARDS has resolved or has been treated. Supportive care in the management of ARDS focuses on mitigating further lung injury that can be induced by

mechanical ventilation. Major clinical trials in the treatment of ARDS have focused on decreasing further lung injury and have found that low tidal volume ventilation with goal plateau pressure of less than 30 mm Hg, as well as prone positioning, decrease mortality.^{25,26} However, the major clinical trials of ARDS have historically included mostly male participants^{25–27} or did not cite sex in the baseline characteristics²⁸ (Table 1).

Gender may impact the management of ARDS. The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE trial) was a multicenter, prospective, observational study of 459 ICUs from 50 countries across 5 continents looking at the epidemiology and patterns of management of patients who met the Berlin criteria for ARDS. Although there were no differences in the recognition of ARDS between the sexes, a secondary analysis of the LUNG-SAFE trial found that women were overall less likely to receive low tidal volume ventilation and were more likely to have higher driving pressures during mechanical ventilation for ARDS. Furthermore, in patients classified as having severe ARDS, women were found to have higher ICU and hospital mortality rates.²⁹ Further analyses of ARDS Network trials revealed that females were twice as likely to receive ventilation

Table 1 Participants by gender in major ARDS clinical trials	
Trial	Participants by Gender
ARMA (Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome)	861 total patients Intervention group (n = 432) 172 women 260 men Control group (n = 429) 175 women 254 men
PROSEVA (Prone Positioning in Severe Acute Respiratory Distress Syndrome)	466 total patients Intervention group (n = 229) 63 women 166 men Control group (n = 237) 85 women 152 men
ACURASYS (Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome)	Not specified
ROSE (Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome)	1006 total patients Intervention group (n = 501) 210 women 291 men Control group (n = 505) 236 women 269 men

with tidal volumes in excess of 6 mL/kg of ideal body weight.^{30,31} This gender inequity in the receipt of higher tidal volumes may simply be a function of shorter height and likelihood of overestimating height, ultimately affecting the application of low tidal volume ventilation.³² There are no conclusive data to demonstrate whether there is sex-related susceptibility to ventilator-induced lung injury.³³ Nonetheless, it is clear that inexact measurements of height with an impact on delivering tidal volumes based on ideal body weight in the treatment of ARDS largely affects women and careful attention should be paid to the management of mechanical ventilation in this subgroup of patients.

One unique subset of female patients affected by ARDS and requiring further special attention is the obstetrics population. Very little literature has focused on the epidemiology and management of ARDS in obstetrics patients, who have also traditionally been excluded from ARDS clinical trials, although ARDS accounts for one of the most common etiologies of maternal death in the ICU.³⁴ Much of obstetrics-specific literature in ARDS resulted from the H1N1 influenza pandemic, in which pregnant women were found to have higher risk of development of complications from influenza A, with an increased rate of serious illness and hospitalization from influenza^{35,36} and mortality rates estimated between 9% and 14%.³⁷ Complications related to pregnancy widen the differential for causes of ARDS, including amniotic fluid embolism, tocolytic-induced pulmonary edema, eclampsia, and puerperal sepsis. The physiologic changes of pregnancy, including decreased chest wall compliance, higher plateau pressures owing to diaphragmatic compression from the gravid uterus, and respiratory alkalosis pose a challenge in the management of ARDS, which often dictates plateau pressures of less than 30 mm Hg and lower tidal volumes with permissive hypercapnia to avoid ventilator-induced lung injury. Unfortunately, there are no clear-cut data on the role of permissive hypercapnia in the pregnant patient and its effect on uteroplacental and umbilical blood flow.

One of the most crucial aspects of ARDS management in the pregnant patient is the timing of delivery, during which the catecholamine surge and significant fluid shifts between the intravascular, intracellular, and interstitial compartments may influence trajectory of ARDS; very little literature examines or reviews the optimal timing of delivery in patients with ARDS.³⁸ Overall, the current literature provides expectant guidance on the management of the obstetrics patients suffering from ARDS, but clinical trials thus far have generally

excluded pregnant patients. The treatment of ARDS in pregnancy is, therefore, extrapolated from the literature in the general population, with exceptions made for the physiologic changes of pregnancy and support for the fetus, including a higher SpO₂ goal of 94% and avoidance of permissive hypercapnia, because hypoxia and acidosis are poorly tolerated by the fetus.³⁹

Overall, sex- and gender-specific literature in ARDS is limited at this time and remains an area requiring further research.

GENDER DIFFERENCES IN SEPSIS AND SEPTIC SHOCK

Sepsis and septic shock, conditions defined by life-threatening organ dysfunction as a result of a dysregulated host response to infection, are common clinical syndromes that require prompt identification and treatment. Multiple studies have attempted to ascertain whether gender differences exist in the presentation, treatment, and outcomes in patients with sepsis and septic shock.

There is some evidence that males are more likely to experience septic shock than females. Campanelli and colleagues⁴⁰ reviewed 36 articles of 498,146 patients and found that males were more likely than females to be admitted to the ICU for septic shock. A review of 1136 admissions by Azkárte and colleagues⁴¹ also showed a male predominance, with 60% to 70% of the septic shock admissions per year being in males over the 6-year study period. A review of ICU admissions for severe sepsis in Italy similarly showed a male preponderance.⁴²

Multiple studies have attempted to determine what sex-based factors may contribute to the risk and outcomes in critical illnesses, including infection and sepsis, with a focus on different hormonal responses, among other factors. Differences in sex hormone levels may be more important than gender alone. Male sex hormones (androgens) have been shown to have some immunosuppressive effects, in contrast with female sex hormones (estradiols), which have shown immunoprotective effects, as summarized by Angele and colleagues⁴³; there remains speculation if therapies used to manipulate hormone status in septic patients could be beneficial, and efforts testing different treatments are ongoing.

Among the few interventions that have shown improved survival in sepsis and septic shock are completion of sepsis bundles⁴⁴ and a short time to the initiation of empiric antibiotics.⁴⁵ Two retrospective cohort studies have found that sepsis bundles were less likely to be completed in the

emergency room if the patient was female.^{46,47} In contrast, the DISPARITY study found no association between gender and bundle completion.⁴⁸ However, the DISPARITY study did find women were less likely to receive antibiotics within 3 hours.⁴⁹ Two other studies have also found that females had a longer time before antibiotic initiation for sepsis.^{47,49} It is unclear why females have a delay to antibiotic initiation in sepsis and septic shock, and further research is needed to determine why there is inconsistency in sepsis and septic shock resuscitative efforts between the sexes.

There may be sex-based differences in mortality from sepsis. One large retrospective cohort study of more than 18,000 ICU patients in Canada, Brazil, and the United States found an increased mortality rate in females, even after adjusting for baseline characteristics.⁵⁰ Similarly, Nachtigall and colleagues⁵¹ found an increase in mortality for female patients admitted to the ICU with sepsis, as did Sakr and colleagues in severe sepsis.⁴² In contrast, other studies have found a male predominance in nonsurvivors of sepsis and septic shock.^{52–54} Multiple other studies have found no difference in mortality between the sexes.^{41,47,55–57} The difference in outcomes may be due to poor baseline characteristic matching; there was significant variability in sample size between the studies thus far. The development of multicenter, prospective registries would eliminate the biases wrought by retrospective studies.

Maternal sepsis is one of the major factors accounting for the admission of pregnant and postpartum patients to the ICU. Sepsis accounts for approximately 23% of all maternal deaths; a retrospective study by Hensley and colleagues⁵⁸ assessing for nationwide incidence and outcomes of maternal sepsis in 27 states in the United States within 42 days of delivery hospitalization discharge from 2013 to 2016 found that 2905 deliveries out of 5,957,678 deliveries were complicated by sepsis (0.04% of deliveries). Risk factors for sepsis in pregnancy include non-White ethnicity, obesity, impaired glucose tolerance and diabetes mellitus, protracted active labor, and prolonged rupture of membranes. Group A *Streptococcus* is one of the most common causes of infections in pregnant and postpartum patients. The immunologic changes of pregnancy to protect the fetus from the maternal inflammatory response includes downregulation of T-cell activity, additionally predisposing the pregnant patient to infections like *Listeria monocytogenes* and more severe manifestations of viral and fungal infections.⁵⁹ The physiologic changes of pregnancy may overlap with the physiologic changes seen in sepsis, leading

clinicians to a late identification of sepsis; this factor, in turn, may result in the late initiation of antibiotics, ultimately impacting morbidity and mortality.

Other differences between sepsis and septic shock outcomes that are sex specific have been observed. In a retrospective cohort study by Pietropaoli and colleagues,⁵⁰ females had a lower likelihood of independence at discharge and had more code status limitations during admission. Both Pietropaoli and colleagues⁵⁰ and Xu and colleagues⁵² found that females were less likely to receive dialysis and invasive ventilation during admission for sepsis and septic shock. Xu and colleagues also found that males were more likely to receive vasopressors. Overall, the trend of these findings is for less aggressive care to be performed in female patients in sepsis and septic shock, although it is unclear if it is because females are less ill as compared with males and do not require aggressive care, if females are choosing to have less aggressive care, or if aggressive measures are not being offered to females. **Table 2** summarizes studies analyzing the gender in the treatment of sepsis.

OUTCOMES AND RESEARCH IN THE CRITICALLY ILL OBSTETRICS AND POSTPARTUM PATIENT

About 200 to 700 women per 100,000 deliveries require ICU admission in the United States.⁶⁰ Maternal mortality rates differ significantly in developing countries than in developed countries; the estimated maternal mortality rate ratio expressed as maternal deaths per 100,000 deliveries is 462 in developing countries versus 11 in developed countries. However, maternal mortality and severe morbidity is rising in the United States and is projected to increase^{61,62} as advanced maternal age poses a risk factor for complications related to pregnancy requiring ICU admission, with the odds of maternal mortality increasing for obstetrics patients older than age 40.⁶³ Additional risk factors for poor outcome in the critically ill obstetrics patients include minority status (specifically, non-Hispanic Black patients) and those with lower socioeconomic status.⁶⁴ These outcomes are further complicated by care of the pregnant patient either by clinicians who are unfamiliar with the management of critically ill obstetrics and postpartum patients or by a lack of multidisciplinary care, including the intensivist.

Research regarding the care of the critically ill obstetrics patient has focused on identifying obstetrics patients at risk of requiring ICU-level care or multidisciplinary care, as well as the establishment of dedicated obstetrics critical care units

Table 2
Treatment differences in sepsis and septic shock in females

Author	Reference	Finding
Mikkelsen et al, 2010	46	Fewer sepsis bundles completed
Sunden-Cullberg et al, 2020	47	Fewer sepsis bundles completed, longer time to antibiotic initiation
Madsen et al, 2014	48	No difference in sepsis bundle completion, longer time to antibiotic initiation
Madsen et al, 2014	49	Longer time to antibiotic initiation
Pietropaoli et al, 2010	50	Less dialysis, less mechanical ventilation
Xu et al, 2019	52	Less dialysis, less mechanical ventilation, less initiation of vasopressors

owing to increasing maternal morbidity and mortality over the last 20 years.

Major maternal morbidity and mortality may be preventable in many cases; multiple reviews in various countries have suggested that up to 50% of maternal deaths are preventable and related to hemorrhage, hypertension, infection, and thromboembolic events.^{65–67} Research of the critically ill obstetrics population in the last decade has focused on the use of early warning systems that can identify obstetrics patients at risk of progressing to critical illness as the physiologic changes of pregnancy may contribute to clinicians underestimating clinical deterioration. Three such scoring systems include the Modified Early Obstetric Warning System (MEOWS, used in the United Kingdom), the Maternal Early Warning Criteria (MERC), and the Maternal Early Warning Trigger (MEWT, used in the United States)⁶⁸ (**Table 3**). A validation study of the MEOWS of 676 obstetrics patients admitted to a single center in the United Kingdom found the implementation of the MEOWS in identifying patients at risk of deterioration to be 89% sensitive, 79% specific, have a positive predictive value of 39%, and negative predictive value of 98%.⁶⁹ The MEWT tool was implemented internally at multiple sites in the Dignity Health System in the United States and prospectively validated; the tool addressed the 4 most common conditions resulting in maternal morbidity: sepsis, cardiopulmonary dysfunction, preeclampsia-hypertension, and hemorrhage. Outcomes measured were the Centers for Disease Control and Prevention–defined severe maternal morbidity, composite maternal morbidity, and

ICU admission before the implementation of MEWT and after the implementation of MEWT. At the pilot sites, the use of the MEWT tool resulted in a significant decrease in severe morbidity as defined by the Centers for Disease Control and Prevention ($P<.01$) and in composite morbidity ($P<.01$); ICU admissions remained unchanged in the period after the implementation of the MEWT tool.⁷⁰ The use of obstetrics early warning systems have overall been shown to rapidly identify obstetrics patients at risk of clinical deterioration to mitigate morbidity; an evaluation of the effectiveness of these tools is ongoing, but preliminary reports suggest a positive impact on outcomes for obstetrics patients.⁷¹

In addition to the implementation of scoring tools to identify patients at risk of progressing to critical illness, a growing area of research in obstetrics critical care is the implementation of obstetrics-specific rapid response teams. The implementation of obstetrics rapid response teams was advocated by the US Department of Health and Human Services along with the American Hospital Association to improve delivery of emergency care on maternity wards. There is also an increasing national initiative by the American College of Obstetrics and Gynecologists, The Institute for Healthcare Improvement, The Joint Commission, and The Agency for Healthcare Research and Quality to implement rapid response teams⁷² for obstetrics wards with translation to improved various patient outcomes, including decreasing ICU admissions and improved outcomes in postpartum hemorrhage.^{73,74} A recent article

Table 3 Comparison of maternal early warning system	
Early Warning System	Triggers for Evaluation
Modified Early Obstetric Warning System (MEOWS)	<p>Either 1 red criterion or 2 yellow criteria must be met to trigger evaluation</p> <p>Red</p> <p>RR <10 or >30</p> <p>SpO₂ <95</p> <p>Temperature <35°C or >38°C</p> <p>SBP <90 mm Hg OR >160 mm Hg</p> <p>DBP >100 mm Hg</p> <p>HR <40 or >120</p> <p>Neurologic response either unresponsive or responsive to pain only</p> <p>Yellow</p> <p>RR 21–30</p> <p>Temperature 35–36°C</p> <p>SBP 90–100 mm Hg OR 150–160 mm Hg</p> <p>DBP 90–100 mm Hg</p> <p>HR 40–50 or 100–120</p> <p>Pain score 2–3</p> <p>Neurologic response to voice only</p>
Maternal Early Warning Criteria	<p>Any of the following criteria should trigger evaluation</p> <p>RR <10 or >30</p> <p>SpO₂ <95 on room air</p> <p>SBP <90 mm Hg or >160 mm Hg</p> <p>DBP >100 mm Hg</p> <p>HR <50 or >120</p> <p>Oliguria <35 mL/kg for >2 h</p>
Maternal Early Warning Trigger	<p>Either 1 red criterion or 2 yellow criteria must be met to trigger evaluation</p> <p>Red</p> <p>RR >30</p> <p>SpO₂ <90%</p> <p>Temperature >38°C</p> <p>SBP >60 mm Hg</p> <p>DBP >110 mm Hg</p> <p>Mean arterial pressure <55 mm Hg</p> <p>HR >130</p> <p>Nursing clinically uncomfortable with patient status</p> <p>Yellow</p> <p>RR <12 or 25–30</p> <p>Temperature <36 C</p> <p>SBP <80 mm Hg OR 156–160 mm Hg</p> <p>DBP <45 mm Hg or 106–110 mm Hg</p> <p>HR <50 or 111–130</p> <p>SpO₂ 90%–93%</p> <p>Altered mental status</p>

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure.

by the obstetrics-specific crisis team at the University of Pittsburgh Medical Center Magee Women’s Hospital outlines the implementation, training, and maintenance of an obstetrics-specific rapid response team; although a detectable impact on the perinatal quality and safety

data could not be ascertained owing to the short lead time between implementation and publication, the implementation of a crisis team familiar with obstetrics is expected to have a positive impact on care of the deteriorating or critically ill obstetrics patient.⁷⁵

An area requiring further research is the impact of obstetrics ICU on maternal outcomes; very limited evidence is available for the establishment of obstetrics-specific critical care units^{76,77}; nonetheless, the pregnant patient is expected to benefit from the establishment of multidisciplinary care with nursing resources dedicated to and familiar with obstetrics and postpartum complications requiring intensive care.

Finally, research regarding outcomes in the critically ill pregnant patient is not complete without commenting on the paucity of clinical trials allowing the inclusion of obstetrics patients. The Institute of Medicine published a report in 1994 recommending that pregnant patients be presumed eligible for inclusion in clinical studies unless there is (1) lack of medical benefit to the pregnant patient and (2) risk of significant harm to the fetus was known or could be plausibly inferred⁷⁸; nonetheless, pregnant women continue to be excluded from pharmacologic trials and the treatment of this population is often inferred from outcomes in critically ill, nonpregnant patients. This has proven particularly problematic during the recent SARS-CoV-2 pandemic, during which obstetrics patients have proven vulnerable but have been excluded from clinical trials thus far. Advancements in the care of the critically ill obstetrics patient remain limited by the exclusion of pregnant patients from clinical trials.

GENDER DIFFERENCES IN INTENSIVE CARE UNIT OUTCOMES

Few studies have definitively concluded whether sex impacts survival in the ICU or functional outcomes after ICU admission. Retrospective studies are conflicting regarding differences in short-term mortality between men and women; although some investigators have concluded that short-term mortality does not differ between the sexes,^{79–81} others have found that the odds of ICU mortality are higher in women and, in particular, women older than 50.⁶ Only 1 prospective study has attempted to delineate long-term outcomes of critically ill patients on the basis of sex; the French and European Outcome Registry in Intensive Care Unit study (FROG-ICU study) was a prospective, multicenter, cohort designed to investigate the long-term mortality of critically ill patients, specifically, the 1-year mortality rate for women compared with men. The study included 2087 patients, 726 of whom were women with similar baseline characteristics and severity illness as compared with male participants. ICU mortality, 28-day mortality, and 1-year mortality did not differ significantly between men and women, even when

adjusting for confounding factors such as comorbidities and severity of illness. Little has been published in regard to the short and long-term outcomes of critically ill patients on the basis of sex.⁸²

Beyond survival, delirium and functional outcomes after critical illness may differ between the sexes, although research is limited in this area as well. Delirium is an acute condition characterized by disturbances in awareness, attention, and cognition that is particularly common in the ICU for many reasons, including the acuity and severity of patient illness, lack of family visitation, loud machines and noises, and frequent interventions. Delirium can have various manifestations, with some patients expressing agitation, impulsivity, and combativeness (hyperactive delirium), whereas others will express somnolence and decreased arousal (hypoactive delirium), and some will have both findings (mixed delirium). Delirium in the ICU has been shown to be associated with higher mortality rates at 6 months after discharge, longer hospital lengths of stay, increased incidence of cognitive impairment at hospital discharge, higher intensive care and overall hospital costs, and worse cognitive and functional impairment at 1 year after discharge.^{83–85}

Given the prevalence and outcomes of delirium, many studies have been performed to evaluate the risk factors of those who develop delirium in the ICU. There is some variability in the literature as to whether there is a true gender predominance in the risk of ICU delirium, but multiple studies have shown no sex differences among patients who did develop delirium.^{86,87} Furthermore, 1 study did not demonstrate any difference between men and women on the duration of ICU delirium.⁸⁸ However, a study in North American surgical and medical ICUs on delirium development in mechanically ventilated patients demonstrated more predominance of delirium in male patients.⁸⁹

There may be sex differences in the subtype of delirium expressed. One review series of a pooled data set demonstrated that female patients were more likely to have a hypoactive delirium subtype as compared with the male patients studied, although this study was not conducted in ICU patients, but rather patients hospitalized in acute medicine settings.⁹⁰ The severity of the delirium in these hospitalized patients was noted to be similar between the sexes. Similarly, a retrospective review series found that male patients in the ICU had higher rates of documented agitation and hyperactive delirium as compared with females.⁹¹ Additionally, the review series found that male patients in the ICU were more likely than females to be initiated on antipsychotics,

presumably because hyperactive symptoms are more visible and invoke more safety concerns as compared with hypoactive symptoms. Similarly, another study on antipsychotic use in the ICU found that males admitted to the ICU were more likely than females to be newly initiated on antipsychotics, although this study did not focus specifically on delirious patients.⁹² However, a different review series concluded there was no difference in ICU delirium subtype among the sexes.⁹³ Overall, the current literature does not demonstrate a consistent sex difference in the risk, duration, or severity of ICU delirium. Female patients who are mechanically ventilated may develop delirium less often as compared with their male counterparts. There may be differences in delirium subtypes expressed between the sexes, with female patients being more likely to express a hypoactive delirium.

Finally, sex- and gender-related disparities in functional outcomes after critical illness are not well-studied. A secondary analysis of the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU survivors (BRAIN-ICU) attempted to examine disparities in functional outcome after a critical illness on the basis of sex; of the 821 participants enrolled in the study, 311 were female. The authors attempted to follow participants to 12 months of follow-up. At baseline, female participants had lower Sequential Organ Failure Assessment scores, but higher baseline depression and disability, as assessed by activities of daily living. At 3 months of follow-up, the female participants were found to have greater odds of activities of daily living disability, worse physical function-related quality of life, more depressive symptoms, more symptoms of post-traumatic stress disorder, and were less likely to be living at home at 3 months than male participants when adjusting for age, comorbidities, and baseline disability. At 12 months, most of these differences were no longer statistically significant, except for trauma symptoms and differences in global physical function, which the authors attributed to loss to follow-up and differences in trajectories of recovery by sex, although this aspect is not explored further. The authors concluded that females were more likely to experience disability, depression, trauma, and short-term institutionalization after critical illness than males.⁹⁴ Previous studies have confirmed susceptibility to physical and psychological impairments in female patients,^{95,96} as well as lower socioeconomic status and a lack of an available caregiver, which impacts the ability to return home after a hospitalization.⁹⁷ These findings have yet to be confirmed by larger scale trials.

SUMMARY

Research on sex differences in critical illness is limited by reduced enrollment of both nonpregnant and pregnant females in clinical trials, retrospective studies, and gender dimorphism in 2 of the most common illnesses requiring intensive care—sepsis and ARDS. Men are admitted to the ICU more commonly than women and use more resources, with research suggesting better functional outcomes than women, although the short- and long-term survival rates are similar. Sex hormones seem to influence the trajectory of critical illness, but outcomes vary depending on the hormone cycle and disease state. Sepsis outcomes do not clearly differ by sex or gender, but women receive less timely treatment. Although males have higher ARDS-related mortality, women are subject to potentially inappropriate and harmful management with little research available on the treatment of the pregnant patients with ARDS. The critically ill obstetrics patients poses a management challenge owing to the physiologic changes of pregnancy and recent research has made efforts to develop obstetrics early warning systems, obstetrics-specific rapid response teams, and obstetrics critical care units to improve delivery of care and outcomes in the critically ill patient. The understanding of sex and gender differences in critical illness is currently limited, but expanded research will allow for increasing application of precision medicine in the ICU.

CLINICS CARE POINTS

- Male patients gain admission to the intensive care unit and utilize resources in the intensive care unit more than female patients.
- Estrogen may have a protective effect in critical illness.
- Women receive less appropriate management of the acute respiratory distress syndrome than men.
- No consistent differences in sepsis outcomes by gender have been found but women receive less timely initiation of antibiotics.
- Women are more likely to experience hypoactive delirium while in the intensive care unit and have worse functional outcomes following discharge.

DISCLOSURE

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